Section A-Research paper
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A systematic review of indications/outcomes of enucleation versus standard pancreaticoduodenectomy for pancreatic neuroendocrine tumors (PNETs)

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ABSTRACT

Background

The medical management of pancreatic neuroendocrine tumors (PNET) relies on several pharmacotherapeutic and surgical interventions. Patients with PNET of small dimensions and tumor location beyond the pancreatic duct require enucleation, while those with large-sized PNET become the candidates for distal pancreatectomy or pancreatoduodenectomy. Recent evidence indicates the possible efficacy of laparoscopic/robotic distal pancreatectomy in PNET management. This study aims to investigate the indications/outcomes of enucleation versus standard pancreaticoduodenectomy/distal pancreatectomy (or routine resection) in patients treated for PNETs.

Methods

This systematic review was undertaken on 1 June 2023 and included studies published between January 2010 and December 2022. Retrospective studies published only in the English language were selected for analysis. The primary endpoint was overall survival (OS), while the secondary outcomes endpoints were operative time, postoperative pancreatic fistula (POPF), morbidity, mortality, length of hospital stay, reoperation, blood loss, relapse-free survival (RFS), reintervention, readmission, and disease-free survival (DFS).

Results

The overall findings revealed no significant differences between the study groups for OS. Importantly, patients with positive node status had an OS rate of 82.1% compared to 89.7% in the negative node group ($p<0.001$). A shorter operative time was observed in patients who received enucleation compared to those with routine resection ($p<0.01$). A higher incidence of POPF was observed after enucleation compared to the routine resection ($p=0.49$). A lower incidence of morbidity was observed in patients with enucleation compared to those who underwent routine resection ($p<0.05$). No to 0.5% postoperative mortality rates were observed in the enucleation group compared to the routine resection group (1.6-14.3%) ($p<0.05$). Comparable hospital stay durations, RFS (≈85%), reinterventions, readmission rates, and DFS (>90%) were observed between the study groups.

Importantly, lower occurrence of reoperation and reduced intraoperative blood loss were observed after enucleation, compared to the routine resection ($p<0.05$).

Conclusion

The findings from this study emphasize enucleation as a viable surgical approach for managing small-sized PNETs since its postoperative outcomes are comparable to the routine resection endpoints. Future studies should investigate the efficacy and safety of enucleation in patients with large-sized PNETs.

Keywords: *Pancreatoduodenectomy, PNET, distal pancreatectomy, routine resection, metastasis, pancreatic neuroendocrine tumors*

INTRODUCTION

The pathological conditions in the diffuse neuroendocrine cells result in the development of highly heterogenous and clinically rare pancreatic neuroendocrine tumors (PNETs); the incidence rate of PNET was 1-2% a few decades back; however, a significant rise is reported in the recent years, particularly in the United States, with the occurrence of $0.43/10^5$ [1, 2]. The diagnostic assessment of PNETs correlates with hormonal secretion, symptomatology, clinical staging, and pathological grading. Further investigations include the evaluation of cytokines, microRNA profiling, multiple transcript assessment, and circulating tumor cell levels. Drug therapies utilized for treating PNET include somatostatin analogs and steroids; however, their therapeutic efficacy is limited to patients with somatostatin receptor (+) expression [3]. Importantly, the curative treatment strategies for patients with PNET include debulking surgeries and routine surgical resection.

Patients with PNET of small dimensions and tumor location beyond the pancreatic duct require enucleation, while those with large-sized PNET become the candidates for distal pancreatectomy, or pancreatoduodenectomy [4]. The PNETs treated by these techniques are usually located in the pancreas tail, corpus, or head. Recent evidence indicates the possible role of PNET debulking in improving the survival time of patients [2]. However, studies do not delineate the possible mechanisms governing vascular reconstruction after complete pancreatoduodenectomy in patients with PNET. Alternatively, pancreatoduodenectomy, debulking, or distal pancreatectomy are contraindicated for PNET with vascular manifestations [5]. A case study revealed no 12-month disease recurrence after pancreatoduodenectomy in a patient with malignant PNET [6].

Recent evidence indicates the possible efficacy of laparoscopic/robotic distal pancreatectomy in PNET management [7]. The locations of PNETs treated with these approaches are the pancreatic tail and body. The potential advantages of these surgical techniques include higher lymph node harvest, greater spleen preservation time, and reduced intraoperative blood loss. The enucleation technique aims to maximize the preservation of the healthy pancreas and resect the benign/low-grade PNETs; postoperative recovery usually takes 7-11 days [4, 8]. The projected advantages of the enucleation technique include faster recovery, shorter hospital duration, reduced operative time, and minimal intraoperative blood loss. However, the anticipated risks include nerve/tissue deterioration, infections, postoperative bleeding, and pancreatic fistula. The enucleation option for PNET management is often utilized to minimize the incidence of major procedural complications after routine pancreatoduodenectomy [9].

Medical literature provides conflicting evidence concerning the benefits versus advantages of enucleation compared to routine resection (i.e., pancreatoduodenectomy/distal pancreatectomy). A recent meta-analysis by Sharma et al. indicates reduced blood loss and shorter operative duration but a higher occurrence of postoperative pancreatic fistula (POPF) after PNET enucleation, compared to the oncologic resection [10]. Other studies indicate no significant differences in long-term results between routine resection and enucleation in the PNET setting [11]. Few studies demonstrate the role of independent prognostic factors, including age, race, distant metastasis, tumor size, and pathological grade on cancer-specific survival (CSS) and overall survival (OS) in patients who undergo routine

resection of PNETs. Alternatively, better outcomes are usually obtained after enucleation in patients with grade-1 tumors, of diameter <4cm [12]. Additionally, subgroup assessments in various studies indicate reduced hospital duration/operation time after minimally invasive enucleation in comparison to open enucleation [8].

Since the contemporary evidence indicates paradoxical findings regarding the short/long-term outcomes of enucleation versus routine resection of PNET, this study aims to collate and analyze recent evidence in this context of informing clinical practice. To the best of our knowledge, this is the first systematic review of its type, analyzing the primary and secondary endpoints (operative/postoperative results) regarding enucleation and routine resection of PNETs.

METHODS

This systematic review complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for pooling evidence and analyzing/interpreting the primary and secondary outcomes [13].

Search Approach

Embase, JSTOR, Google Scholar, Web of Science, SCOPUS, and PubMed Central databases were systematically explored to retrieve studies based on the outcomes of interest. This systematic review was undertaken on 1 June 2023 and included studies published between January 2010 and December 2022. The advanced filters of the corresponding databases were utilized to filter studies describing outcomes of enucleation versus routine resections in patients with PNET. The following search term combinations were categorically constructed via Boolean Operators to retrieve single-center/multicenter retrospective studies providing robust data, aligning with the aims/outcomes of this systematic review: 1) Enucleation AND PNET, 2) Pancreaticoduodenectomy AND PNET, 3) Distal pancreatectomy, 4) PNET AND routine resection, 5) Enucleation OR Pancreaticoduodenectomy OR Distal pancreatectomy AND PNET, and 6) PNET and routine resection OR enucleation. Two independent authors performed the search process, and the discrepancies or conflicts were resolved with mutual discussion.

Inclusion and exclusion parameters

Retrospective studies published only in the English language were selected for analysis. No prospective or randomized controlled studies were included in this systematic review due to the absence of such studies for PNET's surgical management in the scientific literature. Full-text articles, excluding the abstract-only papers and Congressional presentations, were considered for analysis. In addition, case reports, case studies, review papers, meta-analyses, systematic reviews, opinion papers, cohort studies, correspondences, and editorials were excluded from this systematic review.

Data collection and analysis

Two independent authors performed data collection on a preconfigured form and transferred the outcomes of the included studies to an Excel worksheet. The concept of thematic assessment/synthesis was utilized to analyze the primary and secondary outcomes from the included studies and compare their findings [14]. The study themes aligned with the following primary and secondary endpoints: 1) OS (primary endpoint); 2) Operative time, postoperative pancreatic fistula [POPF], morbidity, mortality, length of hospital stay, reoperation, blood loss, relapse-free survival [RFS], reintervention, readmission, and disease-free survival [DFS] (secondary endpoints).

Risk of Bias (ROB)

The ROB assessment was undertaken by Cochrane's Risk of Bias in Non-randomized Studies (ROBINS-1) tool [15]. Two independent authors evaluated ROB based on confounding, judgment, intervention classification, deviations from the desired procedures, missing data, outcome

measurement, result selection, and overall outcomes. Discrepancies in ROB assessment, between the authors, were resolved via the intervention of a third independent author, and by mutual consensus.

RESULTS

A total of 235 records were extracted from PubMed Central, JSTOR, Google Scholar, and Web of Science; 14 additional studies were retrieved from SCOPUS and Embase. One hundred and twenty-six records were finally screened after removing the duplicates. After excluding 74 studies, 52 full-text articles were evaluated for eligibility. Subsequently, 37 full-text articles were discarded due to missing data (n=14), dubious methodology (n=10), duplicity (n=9), inconsistent findings (n=3), and outcome variables other than the outcomes of interest (n=1). Finally, 15 studies were selected for the systematic review (**Figure 1**). **Table 1** comprehensively summarizes the findings from the included studies [4, 11, 12, 16-27].

Table 1: Systematic review

Authors	Sample size	Study design	Study aim	Endpoints	Statistical interventions	Inferences
Altimari et al. 2021 [16]	4083 subjects	A retrospective study	Authors compared outcomes of enucleation and oncologic resection in patients with less than 2cm PNETs	1. The OS rate after 5 years of follow-up 2. Post-resection node (+) disease	The statistical analysis was undertaken via logistic regression, log-rank test, and Fisher's extract test Data for the analysis were obtained from NCDB Study duration: 2004-2016	The node (+) patients had an OS rate of 82.1% versus 89.7% in the node (–) group ($p<0.001$) The enucleation group was comparable with the oncologic resection group for 5-year OS (88.2% versus 88.5%, $p=0.064$) The oncologic resection was followed by the development of node (–) disease in $1/10^{th}$ of the participants Patients with low-grade PNETs had the possibility of greater benefits from enucleation compared to those with high-grade and large-sized tumors, requiring oncologic resection
Beane et al. 2020 [17]	1136 subjects	A retrospective study	Comparative assessment of enucleation versus resection	1. Operative time 2. Transfusions 3. Pancreatic fistulas (postoperative)	The study data were obtained from the American College	Enucleation resulted in a statistically significant reduction in the mean postoperative LOS

			outcomes in patients with PNETs	4. Morbidity 5. Mortality 6. Mean postoperative LOS	of Surgeons-NSQIP dataset (2014-2017) Baseline differences in patients were adjusted via gamma regression and multivariable logistic approaches Outcomes were compared between enucleation (n=127) and distal pancreatectomy (n=712)/ pancreatoduodenectomy (n=297)	compared to resection (5.7 versus 7.2 days; $p<0.01$) No postoperative deaths were reported in patients who underwent enucleation compared to 1.5% in those with resection Lower morbidity was observed in patients after enucleation compared to resection (36.2% versus 48.7%, $p<0.01$) Both study groups (resection versus enucleation) did not differ significantly in terms of postoperative pancreatic fistulas (48.7% versus 36.2%; $p<0.01$)
Casadei et al. 2010 [18]	46 subjects	A single-center prospective study	To compare the outcomes of resection and enucleation in patients with PNETs	1. Postoperative mortality 2. Morbidity 3. Pancreatic fistula 4. Hospital stays 5. Reoperation	Data were statistically analyzed by X^2, Mann-Whitney U, and Fisher exact tests; the Kaplan-Meier actuarial guided the assessment of survival rates, while the log-rank test determined their statistical significance	No statistically significant differences were observed between the study groups for long-term and postoperative outcomes Patients with benign tumors had a low frequency of R0 resection than enucleation ($p=0.009$)
Cauley et al. 2012 [19]	135 subjects	A retrospective study	Comparative evaluation of resection versus enucleation outcomes in patients with PNETs	1. Operative time 2. Operative blood loss 3. Serious morbidity 4. 10-year survival	Statistical analysis of data was undertaken via descriptive statistics; the Kaplan-Meier approach was used to investigate median survival Fisher's exact and Student's t-tests were used to	Patients who underwent pancreatic enucleation had significant improvements in long- and short-term postprocedural outcomes compared to resection Patients with enucleation had a reduced incidence of pancreatic exocrine (2 versus 17%) and endocrine insufficiency (4 versus 17%) and serious morbidity (13% versus 29%) than those

					analyze continuous data for subgroup comparisons	with resection (all $p<0.05$) Compared to resection, enucleation also resulted in reduced incidences of ICU monitoring (20% versus 41%; $p<0.02$); in addition, they also had a reduced extent of operative blood loss (160 versus 691; $p<0.01$) and shorter operative time (183 versus 271 minutes; $p<0.01$)
Chen et al. 2021 [12]	2571 subjects	A retrospective study	To compare the outcomes of enucleation and surgical resection in patients with PNET	1. Long-term prognosis 2. Surgical approach 3. Tumor location 4. Pathological grade of the tumor 5. Diagnosis year 6. Tumor diameter 7. Gender 8. OS 9. CSS	Statistical investigations of data were performed via the two-tailed T-test, log-rank method, and the Kaplan–Meier approach via SPSS Statistics	Enucleation appeared to be the preferred treatment option for patients with a tumor location 3mm above the pancreatic duct, tumor diameter <4cm, and a well-differentiated tumor The OS and CSS in patients with PNET, following surgical resection, were prognosticated by their age, race, distant metastasis, tumor dimensions, pathological grade, tumor location, diagnosis year, and gender
Crippa et al. 2012 [20]	198 subjects	Analyses of data from a prospective database and a retrospective cohort	To evaluate the outcomes and attributes after pancreatic resections and enucleation of PNETs	1. Post-treatment survival 2. Tumor recurrence 3. Operative morbidity	The categorical variables were compared via the Fisher exact and X^2 tests The statistical analyses of the continuous data were undertaken via the Mann-Whitney U test and the T-test	Patients who underwent pancreatic resections had comparatively lower reoperation rates compared with those who were treated by enucleation (1% versus 8.5%, $p=0.02$) Younger age was an independent predictor of the onset of multiple lesions, higher malignancy rates, and type 1 multiple endocrine neoplasias ($p<0.05$) Pancreatic resections resulted in endocrine (4%) and new exocrine (1.5%) insufficiencies

Dong et al. 2020 [21]	276 subjects	A retrospective study	To compare long/short-term results in patients with PNETs and DNETs	1. OS 2. RFS	Mann Whitney test was used to analyze IQR and median values of continuous variables Fisher exact test and x^2 test to compare percentages and totals of the categorical variables The propensity score matching assisted to reduce the selection bias The log-rank test was used to compare RFS and OS, determined by the Kaplan Meier approach	Higher lymph node metastasis rates were observed in those with DNET versus patients with PNET (60% versus 38.2%; p=0.022) RFS and OS were comparable between the study groups despite data adjustments High recurrence rates and extrahepatic manifestations were observed in the DNET group versus the PNET group
Hedges et al. 2022 [22]	3532 subjects	A retrospective study	To establish POPF factors in patients with PNET	1. POPF rate	Statistical analysis of data was undertaken via multinomial/binary logistic regression approach, Student's T-test, and Chi-squared test	Patients without PNET had a significantly low PNET rate compared to those with PNET (16.4% versus 24.8%; p<0.0001) Among PNET patients, POPF rates were independently associated with soft gland texture (OR: 1.81), small duct size (OR: 3.24), pancreaticoduodenectomy (OR: 1.51), enucleation (OR: 3.14), and male gender (OR: 1.45)
Heidsma et al. 2021 [11]	1034 subjects	A retrospective study	To evaluate and compare long-term outcomes between pancreatic enucleation and pancreatoduode	1. POPF 2. RFS	Statistical analyses were performed via descriptive statistics, log-rank test, and Kaplan-Meier approach	Compared to patients who underwent resection, a higher POPF incidence was reported in the enucleation group (24.5% versus 14.0%, p=0.049)

			nectomy			No statistically significant differences were observed between the study groups for median RFS (47 versus 37 months, p=0.480)
Jilesen et al. 2015 [4]	205 subjects	A retrospective study	To compare the postoperative outcomes in patients with standard resections and those with enucleation	1. Overall complications 2. Reinterventions 3. Readmissions 4. Endocrine/exocrine insufficiency	The statistical analyses of the data were performed via the X^2 d test, Mann-Whitney U test, and univariate assessment	Patients who underwent pancreatoduodenectomy had significantly higher endocrine and exocrine insufficiency than those with enucleation (19% versus 7%); the enucleation complications were independently predicted by BMI and tumor location No statistically significant differences were observed between the study groups for readmissions, reinterventions, and overall complications
Nießen et al. 2022 [23]	122 subjects	A retrospective study	To compare the outcomes after formal resection and enucleation in patients with PNET	1. Operative duration 2. Postoperative diabetes 3. Postoperative pancreatic fistula 4. Hospital stay duration 5. OS 6. DFS 7. 30-day mortality 8. POPF 9. Clavien-Dindo ≥ III complications	Statistical analyses of the data were undertaken via the Fisher exact test and Mann-Whitney U test via the R opt-match package	In comparison to formal resection (1.6%), enucleation did not result in 30-day mortality No statistically significant differences were observed between the study groups for DFS (98% versus 91%), 10-year OS (89% versus 77%), hospital stay duration, readmission rate, Clavien-Dindo ≥ III complications, and POPF (all >0.05)
Sallinen et al. 2017 [24]	210 subjects	A retrospective study	To compare outcomes/complications between pancreatoduodenectomy, distal pancreatectomy, median pancreatectomy, and enucleation in patients with non-functional PNET	1. Postoperative mortality 2. Severe morbidity rate 3. Disease recurrence 4. DFS	The statistical analyses of the paired continuous variables were undertaken by the Wilcoxon rank-sum test, while the continuous variables were examined by the Mann–Whitney U-test; the	The postoperative assessment revealed 87.3%, 91.0%, and 95.1% DFS at 5, 3, and 1 years, respectively The disease recurrence was independently determined by pancreatic/biliary duct

					categorical variables were evaluated by the Fisher exact test	dilation and tumor size Overall, the severe morbidity and postoperative mortality rates were 14.3% and 0.5%, respectively The surgical treatment proved beneficial in patients with PNET and grade 2-3 pancreatic/biliary duct dilation
Sutton et al. 2022 [25]	282 subjects	A collaborative, multi-institutional retrospective study	To compare outcomes of open and minimally invasive interventions in patients with PNET	1. RFS 2. DSS 3. Disease recurrence 4. incisional surgical site infections 5. POPF 6. Nodal harvest 7. Reoperations 8. Percutaneous drainage requirement	Statistical analyses were undertaken by independent samples T-test, Chi-squared test, and Fisher's exact test via SPSS-26	At a median follow-up of 50 months, DFS and RFS were 95% and 85%, respectively Worse RFS (OR: 2.78, p=0.04) was associated with T4/T3 tumors, and improved RFS with grade 2 tumors (HR: 0.20, p=0.002) RFS was not associated with minimally invasive resection (p=0.14) The operative approach could not differentiate between percutaneous drainage requirement, reoperations, POPF, and organ space surgical site infections
Weilin et al. 2019 [26]	123 subjects	A retrospective study	To compare short/long-term results of regular pancreatectomy and enucleation in patients with PNET	1. DFS 2. Lymph node metastasis 3. Pathological grade of PNET 4. Blood loss 5. Surgical duration 6. Other postoperative complications	The statistical assessment of data was performed by the Kaplan-Meier method, Manne-Whitney test, Fisher's exact test, Logistic regression, and Cox proportional Hazard approach	Overall, the long-term postoperative outcomes of regular pancreatectomy and enucleation were comparable (p>0.05 Compared to regular pancreatectomy, enucleation resulted in a significant decline in blood loss and surgical duration (both p<0.01)
Yang et al. 2021 [27]	227 subjects	A propensity-score matched, multicenter, retrospective	To compare long/short-term postoperative results in patients treated	1. Operative duration 2. Estimated blood loss 3. Hospital stay duration 4. DFS 5. OS 6. Other postoperative	McNemar's Test, Kaplan-Meier method, Paired two-tailed	Both patient groups did not differ statistically for OS, DFS, hospital stay duration, and other postoperative

		study	for PNET via enucleation versus routine pancreatectomy	complications	t-test, Chi-square test, Mann– Whitney U test and Student's t-test guided the statistical analysis of the clinical data	complications ($p>0.05$) Compared to routine pancreatectomy, marked reductions in estimated blood loss and average operative tenure were observed in patients with enucleation (both $p<0.001$)

BMI, body mass index; CSS, cancer-specific survival ICU, DFS, disease-free survival; DNET, duodenal neuroendocrine tumor; intensive care unit; DSS, disease specific survival; IQR, interquartile range; NCDB, National Cancer Database; LOS, length of stay; OR, odds ratio; OS, overall survival; PNET, pancreatic neuroendocrine tumor; POPF: post-operative pancreatic fistula; RFS, recurrence-free survival

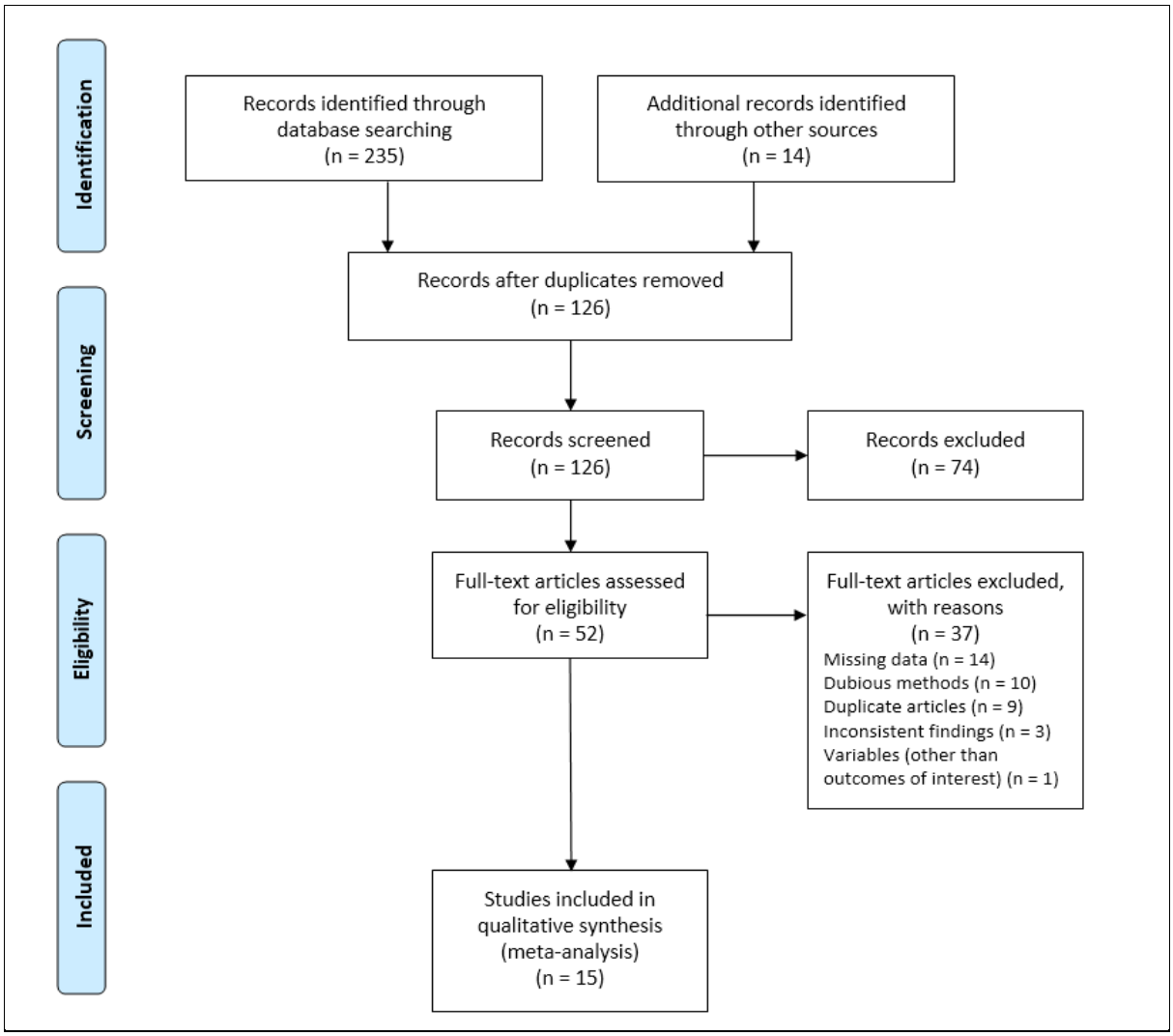

Figure 1 (Study flow diagram)

Overall survival

Four studies statistically compared OS between patients who received enucleation and those with routine resection [12, 16, 21, 27]. The overall findings revealed no significant differences between the study groups for OS. Importantly, patients with node (+) status had an OS rate of 82.1% compared to 89.7% in the node (–) group ($p<0.001$). The prognostic factors for OS in the routine resection group were age, race, distant metastasis, tumor dimensions, pathological grade, tumor location, diagnosis year, and gender. These findings remained consistent in the included studies despite the propensity score data matching.

Operative time

Two studies compared the operative time between the study groups [17, 19]. The pooled results revealed shorter operative time in patients who received enucleation compared to those with routine resection ($p<0.01$).

Postoperative pancreatic fistula

Four studies examined the impact of routine resection versus enucleation on POPF incidence in patients treated for PNET. One study revealed soft gland texture, small duct size, pancreaticoduodenectomy, enucleation, and male gender as the independent prognosticators for POPF development in patients with PNET (all $p<0.05$) [22]. Another study indicated a higher incidence of POPF after enucleation compared to the routine resection ($p=0.49$) [11]. Contrarily, findings by Nießen et al. and Sutton et al. found no statistically significant differences in POPF between the study groups ($p>0.05$) [23, 25].

Morbidity

Five studies compared the occurrences of morbidity or severe morbidity between the study groups [17-20, 24]. Their overall results indicated a lower incidence of morbidity in patients with enucleation compared to those who underwent routine resection ($p<0.05$).

Mortality

Four studies compared mortality rates between patients receiving enucleation and those with routine resection. No to 0.5% postoperative mortality rates were observed in the enucleation group compared to the routine resection group (1.6-14.3%) ($p<0.05$) [17, 18, 23, 24].

Length of hospital stay

The consolidated findings from three studies indicated comparable hospital stay durations between the study groups ($p>0.05$) [18, 23, 27].

Reoperation

The pooled results from three studies indicated a comparatively lower occurrence of reoperation in the routine resection group compared to patients who underwent enucleation ($p<0.05$) [18, 20, 25].

Blood loss

The consolidated outcomes from three studies indicated a significant decline in intraoperative blood loss in patients with enucleation compared to those who underwent routine resection ($p<0.05$) [19, 26, 27].

Relapse-free survival

Findings from three studies indicated comparable RFS (≈85%) between the study groups ($p>0.05$); in addition, the minimally invasive disease did not correlate with RFS ($p=0.14$) [11, 21, 25].

Reinterventions

Patients who underwent routine resection did not statistically differ from those with enucleation in the context of reinterventions (p>0.05) [4].

Readmission

The consolidated results from two studies revealed comparable readmission rates between the study groups, irrespective of tumor attributes and other prognostic factors (p>0.05) [4, 23].

Disease-free survival

The pooled results from four studies indicated no statistically significant differences for DFS (>90%) between the study groups (p>0.05) [23-27]. However, DFS declined with time and ranged between 95% and 87% in patients with enucleation and routine resection.

Risk of Bias

Figure 2 presents the ROB outcomes for the included studies. Overall, 8 studies were associated with low ROB, while only 3 studies had moderate ROB, and 4 studies lacked the desired information for ROB assessment.

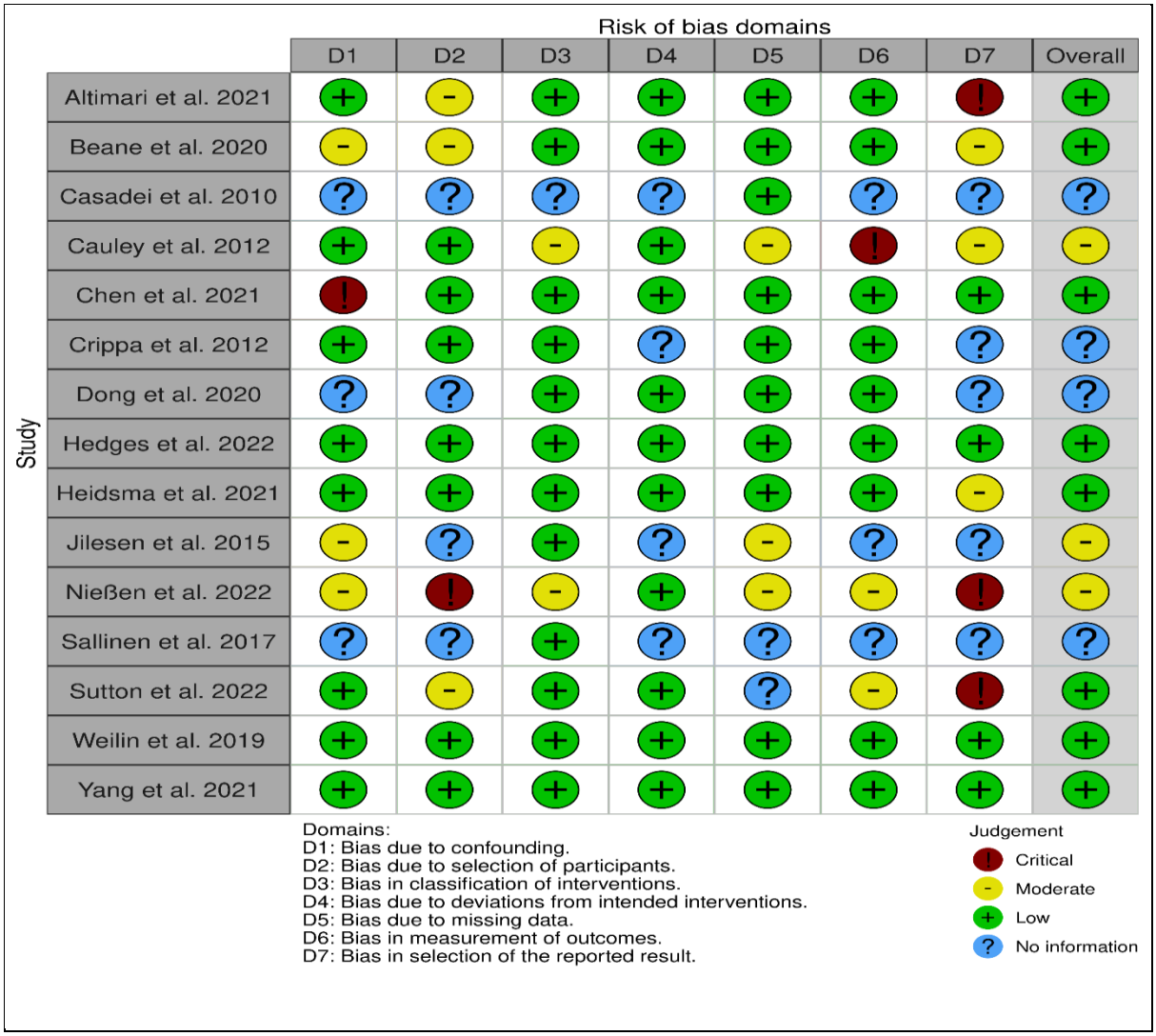

Figure 2 (Risk of Bias)

DISCUSSION

The overall findings of this systematic review indicated comparable OS (82.1-89.7%) between patients who underwent enucleation and those with routine resection; importantly, OS was independently predicted by tumor attributes and demographic characteristics of the patients. The consolidated results revealed the potential of enucleation in minimizing operative time, morbidity, mortality, and intraoperative blood loss compared to pancreatoduodenectomy or distal pancreatectomy. The routine resection; however, was superior to enucleation in terms of reducing reoperation frequency and POPF incidence. The enucleation was comparable with pancreatoduodenectomy for the hospital stay duration, RFS, reinterventions, readmissions, and DFS.

The findings of this systematic review align with the review outcomes of Bartolini et al. that advocate the benefit of enucleation in terms of improving the exocrine and pancreatic endocrine functions, in comparison to routine resection [28]. A recent multi-institutional analysis by Han et al. advocates the selection of enucleation over pancreatoduodenectomy in patients with ≤1.5 cm PNET. The findings further reveal 93.1% RFS and 89.8% OS after 10 years of follow-up in patients who undergo surgical interventions (routine resection/enucleation) for PNET [29]. Our results further strengthen the outcomes of the ACS NSQIP assessment, revealing a 30-day reduction in composite major morbidity in patients with open enucleation compared to the minimally invasive technique [30]. The findings from our study further strengthen the results of Beek et al. indicating the role of major resections in elevating postoperative complications in the PNET setting [31]. Overall, our results add to the current findings in contemporary literature, which endorse the replacement of routine resection with enucleation in small-sized PNETs.

The decision-making regarding the selection of enucleation versus pancreatoduodenectomy in PNET cases warrants multidisciplinary staff meetings, while the diagnostic assessments should ascertain the appropriate staging, grading, localization, and precise measurement of the dimensions of PNET [32]. The surgical management of symptomatic and non-functional tumors is warranted, irrespective of the tumor dimensions. In addition, asymptomatic PNETs of size greater than 2cm also require surgical interventions. It is important to note that unresectable distant metastasis emanating from sporadic functional PNET does not require surgical management [33]. The non-functional PNETs of size below 2cm can be managed with parenchyma-sparing surgery. The predominant prognostic factors for PNET, impacting the survival of patients with PNET, include the 2010 World Health Organization (WHO) Classification, patient age, tumor location, tumor dimensions, mitotic/Ki-67 proliferation index, and PNET's histological type. The latest evidence reveals the 7-year recurrence and survival rates of 24% and 66%, respectively, in patients with PNET, who are treated with surgical interventions [33].

LIMITATIONS

The systematic review has many potential limitations that restrict the generalization of its outcomes in oncology settings. First, the findings from this study did not compare long- versus short-term outcomes of enucleation and routine resections in the PNET setting. Second, the lack of statistical analysis of the pooled findings restricted their overall reliability. Third, the absence of randomized controlled studies based on our study's objective further increases the risk of selection bias and reduces the validity of results. Fourth, we did not categorize findings based on the follow-up durations, due to limited data. Fifth, several inconsistencies in postprocedural surveillance, procedural approaches, surgery indications, and patient selection approaches in the included studies also reduce the overall generalizability of results.

CONCLUSIONS

The results of this study advocate the replacement of complete/minimally invasive pancreatoduodenectomy or distal pancreatectomy procedures in patients, diagnosed with small-sized PNET. The consolidated outcomes reveal comparable OS, hospital stay duration, RFS, reintervention,

readmission, and DFS after enucleation versus routine resection. Importantly, several studies have emphasized the benefits of enucleation over routine resection based on significant improvements in operative time, morbidity, mortality, and intraoperative blood loss. However, pancreatoduodenectomy is still preferred over enucleation for treating large-sized PNETs, and due to its potential to minimize the postoperative incidence of reoperation and POPF. Future randomized-controlled trials should reinvestigate our results with larger sample sizes to improve the medical decision-making concerning the operative management of PNETs and to enhance the overall survival and health-related quality of life of the treated patients.

REFERENCES

1. Sun J: Pancreatic neuroendocrine tumors. Intractable & Rare Diseases Research. 2017, 6:21-8. 10.5582/irdr.2017.01007
2. Chawla A, Williams RT, Sich N, et al.: Pancreaticoduodenectomy and metastasectomy for metastatic pancreatic neuroendocrine tumors. J Surg Oncol. 2018, 118:983-90. 10.1002/jso.25219
3. Ma ZY, Gong YF, Zhuang HK, et al.: Pancreatic neuroendocrine tumors: A review of serum biomarkers, staging, and management. World J Gastroenterol. 2020, 26:2305-22. 10.3748/wjg.v26.i19.2305.
4. Jilesen AP, van Eijck CH, Buschn OR, et al.: Postoperative Outcomes of Enucleation and Standard Resections in Patients with a Pancreatic Neuroendocrine Tumor. World J Surg. 2015, 40:715-28. 10.1007/s00268-015-3341-9.
5. Li AY, Visser BC, Dua MM: Surgical Indications and Outcomes of Resection for Pancreatic Neuroendocrine Tumors with Vascular Involvement. Cancers. 2022, 14:2312. 10.3390/cancers14092312
6. Ochiai T, Masuda T, Nishizawa M, et al.: Curative resection of a huge malignant pancreatic endocrine tumor by pancreatoduodenectomy with the portal and superior mesenteric vein resection and reconstruction using the right ovarian vein: Report of a case. Surg Today. 2011, 41:1260-5. 10.1007/s00595-010-4466-y
7. Zhang J, Jin J, Chen S, et al.: Minimally invasive distal pancreatectomy for PNETs: laparoscopic or robotic approach?. Oncotarget. 2017, 8:33872-33883. 10.18632/oncotarget.17513
8. Zhou Y, Zhao M, Wu L, et al.: Short- and long-term outcomes after enucleation of pancreatic tumors: An evidence-based assessment. Pancreatology. 2016, 16:1092-8. 10.1016/j.pan.2016.07.006.
9. Hackert T, Hinz U, Fritz S, et al.: Enucleation in pancreatic surgery: indications, technique, and outcome compared to standard pancreatic resections. Langenbecks Arch Surg. 2011, 396:1197-203. 10.1007/s00423-011-0801-z.
10. Jilesen AP, Van Eijck CH, Busch OR, et al.: Postoperative Outcomes of Enucleation and Standard Resections in Patients with a Pancreatic Neuroendocrine Tumor. . World J Surg . 2016, 40:715-28. 10.1007/s00268-015-3341-9
11. Heidsma CM, Tsilimigras DI, van Dieren S, et al.: Indications and outcomes of enucleation versus formal pancreatectomy for pancreatic neuroendocrine tumors. Hpb. 2021, 23:413-21. 10.1016/j.hpb.2020.06.015
12. Chen J, Yang Y, Liu Y, et al.: Prognosis analysis of patients with pancreatic neuroendocrine tumors after surgical resection and the application of enucleation. World J of Surg Oncol. 2021, 19:11. 10.1186/s12957-020-02115-z.
13. Page MJ, McKenzie JE, Bossuyt PM, et al.: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. . BMJ. 2021, 372:n71. 10.1136/bmj.n71
14. Newington L, Wells M, Adonis A, et al.: A qualitative systematic review and thematic synthesis exploring the impacts of clinical academic activity by healthcare professionals outside medicine. BMC Health Services Research. 2021, 21:400. 10.1186/s12913-021-06354-y

15. Sterne JA, Hernán MA, Reeves BC, et al.: ROBINS-I: a tool for assessing the risk of bias in non-randomized studies of interventions. . BMJ. 2016, 355:i4919. 10.1136/bmj.i4919
16. Altimari M, Abad J, Chawla A: The role of oncologic resection and enucleation for small pancreatic neuroendocrine tumors. HPB. 2021, 23:1533-40. 10.1016/j.hpb.2021.03.005.
17. Beane JD, Borrebach JD, Billderback A, et al.: Small pancreatic neuroendocrine tumors: Resect or enucleate? . Am J Surg. 2021, 222:29-34. 10.1016/j.amjsurg.2020.12.013
18. Casadei R, Ricci C, Rega D, et al.: Pancreatic Endocrine Tumors Less Than 4 cm in Diameter. Pancreas. 2010, 39:825-8. 10.1097/MPA.0b013e3181cf155c
19. Cauley CE, Pitt HA, Ziegler KM, et al.: Pancreatic Enucleation: Improved Outcomes Compared to Resection. J Gastrointest Surg. 2012, 16:1347-53. 10.1007/s11605-012-1893-7
20. Crippa, S: Surgical management of insulinomas: short- and long-term outcomes after enucleations and pancreatic resections. Arch Surg. 2012, 147:261-6.
21. Dong DH, Zhang XF, Lopez-Aguiar AG, et al.: Surgical outcomes of patients with duodenal vs pancreatic neuroendocrine tumors following pancreatoduodenectomy. J Surg Oncol. 2020, 122:442-9. 10.1002/jso.25978.
22. Hedges EA, Khan TM, Babic B, et al.: Predictors of post-operative pancreatic fistula formation in pancreatic neuroendocrine tumors: A national surgical quality improvement program analysis. . Am J Surg. 2022, 224:1256-61. 10.1016/j.amjsurg.2022.07.007
23. Nießen A, Bechtiger FA, Hinz U, et al.: Enucleation Is a Feasible Procedure for Well-Differentiated pNEN—A Matched Pair Analysis. Cancers (Basel). 2022, 14:2570. 10.3390/cancers14102570
24. Sallinen VJ, Le Large TYS, Tieftrunk E, et al.: Prognosis of sporadic resected small (≤2 cm) nonfunctional pancreatic neuroendocrine tumors - a multi-institutional study. HPB. 2018, 20:251-9. 10.1016/j.hpb.2017.08.034
25. Sutton TL, Pommier RF, Mayo SC, et al.: Similar Outcomes in Minimally Invasive versus Open Management of Primary Pancreatic Neuroendocrine Tumors: A Regional, Multi-Institutional Collaborative Analysis. Cancers. 2022, 14:1387. 10.3390/cancers14061387
26. Weilin M, Xu H, Yang L, et al.: Propensity score-matched analysis of clinical outcome after enucleation versus regular pancreatectomy in patients with small non-functional pancreatic neuroendocrine tumors. Pancreatology. 2020, 20:169-176. 10.1016/j.pan.2019.12.007
27. Yang Z, Gao H, Lu J, et al.: Comparison of clinical outcomes between enucleation and regular pancreatectomy in patients with non-functional pancreatic neuroendocrine tumors: a retrospective multicenter and propensity score-matched study. Jpn J Clin Oncol. 2021, 51:595-603. 10.1093/jjco/hyaa246
28. Bartolini I, Bencini L, Risaliti M, et al.: Current Management of Pancreatic Neuroendocrine Tumors: From Demolitive Surgery to Observation. Gastroenterol Res Pract. 2018, 2018:9647247. 10.1155/2018/9647247.
29. Han IW, Park J, Park EY, et al.: Fate of Surgical Patients with Small Nonfunctioning Pancreatic Neuroendocrine Tumors: An International Study Using Multi-Institutional Registries. Cancers (Basel). 2022, 14:1038.. 10.3390/cancers14041038.
30. Ore AS, Klompmaker S, Stackhouse K, et al.: Does surgical approach affect outcomes of enucleation for benign and low-grade pancreatic tumors? An ACS-NSQIP evaluation. HPB. 2019, 21:1585-91. 10.1016/j.hpb.2019.03.375
31. van Beek DJ, Takkenkamp TJ, Wong-Lun-Hing EM, et al.: Risk factors for complications after surgery for pancreatic neuroendocrine tumors. Surg. 2022, 172:127-36. 10.1016/j.surg.2022.02.007
32. Souche R, Hobeika C, Hain E, et al.: Surgical Management of Neuroendocrine Tumours of the Pancreas. J Clin Med . 2020, 9:2993. 10.3390/jcm9092993.
33. Sánchez-Bueno F, Rodríguez González JM, Torres Salmerón G, et al.: Prognostic Factors in Resected Pancreatic Neuroendocrine Tumours: Experience in 95 Patients. Cirugía Española . 2016, 94:473-80. 10.1016/j.ciresp.2016.05.010